REMARKS

Applicants thank the Examiner for clarifying the previous action.

Applicants canceled claims 8 and 22-34. Claims 2, 3, 12-21 and 35-38 (attached), of which claims 2, 12, and 35 are in independent form, are presented for examination. All the claims require a bone graft substitute composition having a calcium sulfate, a mixing solution, a cellulose derivative, and demineralized bone matrix.

The Examiner rejected claims 2, 3, 12-21, and 35-38 under 35 U.S.C. §103(a) as being unpatentable over the combined teachings of U.S. Patent No. 5,484,601 (O'Leary), U.S. Patent No. 5,385,887 (Yim), and U.S. Patent No. 6,030,635 (Gertzman) taken as a whole. It appears, however, that rejection of the independent claims (2, 12,and 35) is based on a combination of only O'Leary and Yim in which the Examiner relied on O'Leary for disclosing a mixing solution, a cellulose derivative, and demineralized bone matrix, and Yim for disclosing calcium sulfate.

While the Examiner acknowledged that O'Leary does not explicitly disclose adding calcium sulfate to its composition, the Examiner "noted that the O'Leary patent clearly teaches that 'any variety of substances' can be introduced to the composition include 'inorganic elements'."[1] That is, the Examiner reasons that O'Leary's mention of inorganic elements is sufficient motivation to add calcium sulfate to O'Leary's composition.

The Examiner has taken O'Leary's disclosure out of context. In disclosing inorganic elements, O'Leary states:

> Any of a variety of substances can be introduced into the bone particles, e.g., by soaking or immersing the bone particles in a solution of the desired substance(s) followed by drying of the bone particles. Substances which can be readily incorporated in the bone particles in this or any other suitable manner include antiviral drugs, e.g., those suitable for preventing transmission of acquired immune deficiency syndrome (AIDS); antimicrobials and/or antibiotics such as erythromycin, bacitracin, neomycin, penicillin, polymyxin B, tetracyclines, viomycin, chloromycetin and streptomycins, cefazolin, ampicillin, tobramycin, clindamycin and gentamycin, etc.; amino acids, peptides, vitamins, inorganic elements, co-factors for protein synthesis; hormones; endocrine tissue or tissue fragments; synthesizers; enzymes such as collagenase, peptidases, oxidases, etc.; polymer-cell scaffolds with parenchymal cells; angiogenic drugs and polymeric

[1] Page 5 of the Office Action.

> carriers containing such drugs; collagen lattices; biocompatible surface active agents; antigenic agents; cytoskeletal agents; biologically active components such as bone morphogenetic proteins (BMPs), transforming growth factor (TCF-beta), insulin-like growth factor (IGD-1); mesenchymal elements; bone digesters; antitumor agents; cellular attractants and attachment agents; immunosuppressants; permeation enhancers, e.g., fatty acid esters such as the laurate, myristate and stearate monoesters of polyethylene glycol, enamine derivatives, alpha-keto aldehydes, etc.; and, nucleic acids. The amounts of optionally added substances can vary widely with optimum levels being readily determined in a specific case by routine experimentation.[2]

O'Leary's ambiguous mention of inorganic elements provides no indication or suggestion that calcium sulfate is an inorganic element that should be added to O'Leary's composition. Instead, when read in the context of the paragraph above, it appears that the inorganic elements, like the other substances listed above, should have a biological function or be bioactive. But as acknowledged by the Examiner, Yim discloses that calcium sulfate is used to reduce setup time and to provide improved moldability and consistency of the resulting formulation.[3] Yim does not disclose or suggest using calcium sulfate to provide a biological function or activity. Thus, looking at the references in context to determine what they disclose and suggest about the particular components, the Examiner's reliance on "inorganic elements" as suggesting calcium sulfate lacks a reasonable basis.

The Examiner also asserted that since O'Leary and Yim have the same object in creating a malleable, workable bone growth promoting composition, one skilled in the art would have been motivated to include calcium sulfate into O'Leary's composition. Furthermore, the Examiner asserted that since the compositions of Yim and O'Leary are sufficiently similar, one skilled in the art would be aware that calcium sulfate hemihydrate would not impair or otherwise negatively affect O'Leary composition.

Applicants previously responded as to why one skilled in the art would not be motivated to combine the calcium sulfate of Yim with O'Leary's composition, namely, that the reasons that Yim discloses for adding calcium sulfate are either inconsistent with the type of compositions that O'Leary intended to form or that the reasons have already been addressed by O'Leary. Since

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[2] O'Leary, col. 2, line 53, to col. 3, line 14.
[3] Yim, col. 2, lines 63-65.

the Examiner did not respond to Applicants' previous arguments, Applicants will summarize the arguments below.

O'Leary describes flowable demineralized bone powder compositions capable of having widely varying consistency. As specifically defined by O'Leary, the term "flowable"

> applies to compositions whose consistencies range from those which can be described as shape-sustaining but readily deformable, e.g., those which behave like putty, to those which are runny. Specific forms of flowable bone powder compositions include cakes, pastes, creams and fillers.[4]

To provide a flowable material, O'Leary combines the bone powder with a liquid synthetic organic material, e.g., glycerol, that functions as a carrier or suspension agent.[5] In cases where the composition can quickly or prematurely separate from the carrier or settle out from the composition such that application of the composition is difficult or inconvenient, O'Leary discloses adding a thickener, such as polyvinyl alcohol or a cellulosic material, to change the thixotropic and suspension-keeping characteristics (e.g., consistency) of the composition.[6]

As acknowledged by the Examiner, Yim discloses adding calcium sulfate to a composition to improve retention of the composition at a wound site, to reduce formulation setup time, to improve osteoconduction, to reduce preparation time, to improve moldability and handling characteristics, and to improve consistency.[7] As mentioned above, these reasons for adding calcium sulfate are either inconsistent with the type of compositions that O'Leary intended to form or have already been addressed by O'Leary.

For example, improving retention of the composition at the wound site and reducing formulation setup time suggest that the composition should be relatively viscous (so that it could be retained) in a relatively short time (i.e., reduced setup time). However, as clearly defined by O'Leary, in some embodiments, the compositions are intended to be "runny," which suggests relatively low viscosity and relatively long setup time. In embodiments where O'Leary's compositions are intended to be like a putty (e.g., for improved retention and setup time),

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[4] O'Leary col. 3, l. 30-36.
[5] *Id.* col. 3, l. 15-20.
[6] *Id.* col. 3, l. 55 - col. 4, l. 6.
[7] Yim col. 2, l. 51-65; and col. 7, l. 50-59.

O'Leary disclosed adding a thickener such as a cellulosic material. One skilled in the art would not be motivated to further add Yim's calcium sulfate because that would be unnecessarily redundant, and as a result, there is no motivation to form Applicants' claimed composition.

What is more, O'Leary already addressed all the other reasons Yim disclosed for adding calcium sulfate. For example, O'Leary addressed improved osteoconduction by disclosing that glycerol is a preferred carrier because it "exhibits a particularly pronounced capability for dissolving osteogenic proteins present in the bone powder and enhancing the availability of these proteins at the bone repair site."[8] Yim, however, does not disclose that calcium sulfate improves osteoconduction when used as a carrier for a material such as demineralized bone. O'Leary addressed reduced preparation time by disclosing that the carrier includes organic materials that are flowable liquids at ambient temperatures to provide a flowable material of widely varying consistency; on the other hand, calcium sulfate is a powder to which a solubilizing liquid is added, which can increase preparation time. As discussed above, O'Leary expressly disclosed the compositions as being handle-able and moldable ("shape-sustaining but readily deformable"), as well as having improved consistency (the consistencies range, e.g., from "those which behave like putty to those which are runny"). O'Leary explicitly disclosed that a thickener can be added to make the composition easier and more convenient to apply. Therefore, since O'Leary addressed all of Yim's reasons for adding calcium sulfate, one skilled in the art would not be motivated to further add the calcium sulfate. In other words, there is no teaching, suggestion, or incentive to make the combination as suggested by the Examiner.

Furthermore, one skilled in the art reading Yim would not be motivated to combine demineralized bone to Yim's composition. Yim disclosed compositions wherein osteogenic proteins are utilized in the form of a pharmaceutically acceptable ***solution*** (including reconstitution from a lyophilized form). In particular, Yim disclosed that

> It is optimal to solubilize the osteogenic protein at concentrations of at least about 1 mg/ml, preferably about 2 to 8 mg/ml, so that a pharmaceutically effective amount of protein can be delivered without undue volumes of carrier being necessary.[9]

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[8] O'Leary col. 3, l. 49-52.
[9] Yim col. 3, l. 34-39 (emphasis added).

Yim further disclosed that to prevent formation of particulates, a non-ionic surfactant can be added to the composition.[10]

One skilled in the art reading Yim would not be motivated to add demineralized bone material (a source of osteogenic proteins) to Yim's compositions. Demineralized bone is not in the form of a pharmaceutically acceptable solution. Instead, demineralized bone is formed as ***solid particles***, which Yim expressly wanted to eliminate. Thus, one skilled in the art reading Yim would not be motivated to combine demineralized bone matrix to Yim's composition.

Claim 12, which recites a composition having a certain concentrations of components, is patentable for at least the same reasons discussed above. Applicants also note that neither O'Leary nor Yim disclosed or suggested a composition having the claimed concentrations of components.

Turning now to Gertzman, the Examiner relied on Gertzman for disclosing a bone allograft as recited in claim 21. Claim 21, however, depends from claim 2 or 12, and is patentable for at least the same reasons that claims 2 and 12 are patentable over the cited references. Applicants note that Gertzman does not cure the deficiencies of the combination of O'Leary and Yim since Gertzman teaches away from using calcium sulfate in a bone composition. Gertzman discloses that calcium sulfate does not absorb or become remodeled into natural bone so it consequently remains in place indefinitely as a brittle, foreign body in a patient's tissue.[11] So instead, Gertzman discloses using hydrogels that absorb more quickly and allow a bone defect to be remodeled into the natural bone of a patient.[12]

The Examiner rejected claims 8, 22-24, and 28-34 under 35 U.S.C. §103(a) as being unpatentable over the combined teachings of O'Leary, Yim, and Gertzman taken as a whole. Applicants canceled claims 8 and 22-34, and therefore, the rejection should be withdrawn.

In light of the above remarks, Applicants submit that the claims are in condition for allowance, which action is requested.

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[10] *Id.* col. 4, l. 2-7.
[11] Gertzman, col. 1, lines 42-47.
[12] *Id.* col. 4, lines 24-29.

Enclosed is a Petition for Extension of Time and the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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Pending Claims

2. (Twice Amended) A bone graft substitute composition comprising:
(a) calcium sulfate;
(b) a mixing solution;
(c) a cellulose derivative; and
(d) demineralized bone matrix.

3. (Amended) The bone graft substitute composition of claim 2, comprising approximately 40% demineralized bone matrix by dry weight.

12. (Twice Amended) A bone graft substitute composition comprising:
(a) approximately 80-120 parts medical grade calcium sulfate hemihydrate by weight;
(b) approximately 21-250 parts sterile water by weight;
(c) approximately l-40 parts carboxymethylcellulose by weight; and
(d) approximately l0-100 parts demineralized bone matrix by weight.

13. The bone graft substitute composition of claim 2, wherein the mixing solution is selected from a group consisting of sterile water, an inorganic salt, and a cationic surface active agent.

14. The bone graft substitute composition of claim 13, wherein the cationic surface agent is selected from a group consisting of sodium chloride, phosphate buffered saline, potassium chloride, sodium sulfate, ammonium sulfate, ammonium acetate, and sodium acetate.

15. The bone graft substitute composition of claim 2, wherein the mixing solution comprises sterile water.

16. The bone graft substitute composition of claim 2, wherein the cellulose derivative is selected from a group consisting of sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, hydroxyethylcellulose and cellulose acetate butyrate.

17. The bone graft substitute composition of claim 2, wherein the cellulose derivative comprises carboxymethylcellulose.

18. The bone graft substitute composition of claim 2, wherein the calcium sulfate comprises calcium sulfate hemihydrate.

19. The bone graft substitute composition of claim 2, wherein the calcium sulfate comprises calcium sulfate hemihydrate, the mixing solution comprises sterile water, and the plasticizing substance comprises carboxymethylcellulose.

20. The bone graft substitute composition of claim 19, comprising approximately 100 parts calcium sulfate hemihydrate by weight, approximately 11.1 parts carboxymethylcellulose by weight, approximately 162 parts water by weight, and approximately 69.4 parts demineralized bone matrix by weight.

21. The bone graft substitute composition of any one of claims 2, 3, and 12-20, further comprising a bone allograft.

35. A method of making a bone graft substitute composition, the method comprising:

providing a first composition comprising calcium sulfate, a cellulose derivative and demineralized bone matrix; and

contacting the first composition with a mixing solution to form the bone graft substitute composition.

36. The method of claim 35, wherein the first composition further comprises a bone allograft.

37. The method of claim 35, further comprising forming the bone graft substitute composition into a putty.

38. The method of claim 35 wherein the calcium sulfate comprises calcium sulfate hemihydrate, the cellulose derivative comprises carboxymethylcellulose, and the mixing solution comprises sterile water.